REMARKS

Claims 1-22, 33, 34 and 45 are pending in the application. Claims 23-32, 35-44 and 46 have been cancelled as a result of an earlier restriction requirement. By the foregoing amendment, Claims 1, 2, 22, 34 and 45 have been amended, Claims 8 and 9 have been cancelled, and new Claims 47-62 have been added.

Claim Amendments and Additions

Claims 1 and 45 have been amended to more clearly define the invention by incorporating a dimensional aspect into each of these independent claims as well as by clarifying that the microcapsules comprise the antimicrobial agent "dispersed" in the hydrophilic polymer whose water absorption, at equilibrium, is at least about 5% by weight. Applicants have made the latter change to ensure that the claim is not too narrowly misconstrued as applying only to individual particles of the antimicrobial agent which are coated or encapsulated with the hydrophilic polymer, much like an M&M. Indeed, as set forth throughout the specification (see e.g., Page 4, lines 16-18 and Page 16, lines 7-19), the antimicrobial agent and hydrophilic polymer are mixed or compounded together, thereby ***dispersing*** the particles in the polymer matrix. This change also ensures that those embodiments wherein the high aspect ratio microcapsules are made by "slitting, chopping, or cutting" a film, for example, are also covered since in these embodiments there may be particles of the antimicrobial agent that are exposed at the surface of the microcapsule and, thus, are not fully coated or encapsulated (see Page 16, lines 15-16). The water absorption limitation is added to give better clarity and definition as to what Applicants consider hydrophilic.

Claim 2 has been amended to correct a lack of antecedent basis for the term "inorganic".

Claim 22 has been amended to make it consistent with amended independent Claim 1 from which it depends.

Claim 34 has been amended to change the dependency thereof.

New claims 47-54 merely provide dependent claims which incorporate further limitations on the dimensional aspects of the microcapsules according to the present invention. No new matter is entered as these parameters are set forth in the specification at Page 5, lines 20-22 and Page 15, lines 4-7.

New independent claim 55 and its dependent claims 56-62 define a narrow subset of the invention claimed by claim 1. Independent claim 55 sets forth specific limitations relative to the size and aspect ratio of the microcapsules, the weight ratio of the hydrophilic polymer to the antimicrobial agent and the definition of hydrophilic polymers. The remaining dependent claims, claims 56-62 provide even further narrowing and definition to the claimed microcapsules. All of these limitations are fully supported by the specification as well as the original claims.

Claim Rejections – Section 103: Trogolo et. al.

Pursuant to the November 1, 2004 Final Office Action, all claims, namely claims 1-18, 22, 33 and 45 remain rejected under 35 USC §103(a) as being unpatentable over Trogolo et. al. (US 6,436,422). Trogolo et. al. is again cited as allegedly showing combinations of antimicrobial agents, particularly those of the ion-exchange type, with hydrophilic materials and, optionally, a discoloration agent and the use thereof in the coating of, among other substrates, medical devices. The Patent Office asserts that while the reference is silent as to the aspect ratio, a difference in the aspect ratio, in the absence of evidence of criticality, would not support patentability. In following, the Patent Office asserts that Trogolo et. al. disclose similar microcapsules as desired by Applicants including sheets, fibers and cylinders and, in this regard, addresses Applicants' attention to Figure 1 and Col. 5 of Trogolo et. al. The Patent Office concludes that it would have been obvious to one skilled in the art to have modified the microcapsules (of Trogolo) to determine a suitable aspect ratio to achieve the desired results.

Applicants respectfully traverse the rejection and request reconsideration. While the Patent Office is correct in its assessment of Trogolo et. al. as teaching coating compositions comprising an antimicrobial agent in a hydrophilic polymer, and while it may be possible, though not preferable, to use like compositions in forming the microcapsules of the present invention, nothing in Trogolo et. al. suggests or infers that one do so, i.e., make discrete micro-sized particles of its cured or hardened coating compositions. When the coatings of Trogolo et. al. are applied to a substrate they form a continuous layer thereon, said layer matching the overall dimensions of the underlying substrate. To make Applicants' microcapsules from those compositions, one would have to cast a film of the coating composition, cure it and then chop it to the proper dimensional size. Nothing in the art cited by the Patent Office points to or suggests

such a process or outcome. Furthermore, nothing in Trogolo et. al. motivates, suggests, or infers that one could then take those micro-sized particles of its hardened or cured coating composition and add that to other coatings and/or polymer compositions in order to impart antimicrobial characteristics thereto and certainly not to provide markedly enhanced antimicrobial characteristics to such coatings and polymer compositions, especially to such coatings and compositions which are non-hydrophilic, as compared to such coatings and compositions where the antimicrobial agent is not encapsulated.

Though the Patent Office states that "Trogolo discloses the similar coated particles as desired by Applicants", the Patent Office provides no reference to such a teaching. It is true that Trogolo et. al. teach one to coat objects or articles of various shapes and sizes with their antimicrobial hydrophilic coating, including sheets, fibers and cylinders, particularly medical devices; however, no mention is made of coated particles, and certainly not microparticles. Furthermore, contrary to the inference of the Patent Office, Applicants are not coating microparticles with an antimicrobial hydrophilic coating; rather, they are making microparticles which comprise the antimicrobial agent dispersed in a hydrophilic polymer matrix. And, while Trogolo et. al. are making antimicrobial hydrophilic coatings to be applied to various pre-formed objects and articles, as noted above, Applicants are making additives for incorporation into coatings to be applied to such pre-formed articles and into various polymer compositions from which such pre-formed articles may be made. Indeed, the encapsulated antimicrobial microparticles of the present invention could be used in making the hydrophilic coatings of Trogolo et. al. Further, with respect to the aforementioned polymer compositions, since the antimicrobial agent is in the polymer composition from which the article is made, there would be no need for subsequently applying a hydrophilic antimicrobial coating.

As claimed, Applicants' additives comprise microparticles of antimicrobial agents dispersed in a hydrophilic polymer matrix. These additives can be incorporated into hydrophilic or non-hydrophilic polymers, coatings and the like so as to impart antimicrobial efficacy to the same. As discussed in the specification, when the antimicrobial additives of the present invention are incorporated into a non-hydrophilic polymer, they markedly enhance antimicrobial efficacy with little if any adverse impact on the polymer into which they are incorporated.

Similarly, when incorporated into a hydrophilic polymer, they regulate the rate or release of the antimicrobial agent so as to enhance antimicrobial efficacy and/or longevity.

Though experimental data supporting the foregoing performance claims were not included in the instant application as filed, analogous data was subsequently generated and is presented in International Patent Publication No. WO03055941 (PCT/US02/39709), the International equivalent to Applicants' copending United States patent application USSN 10/032,372 filed concurrently with the instant application, a copy of which is herewith submitted with the co-filed Supplemental Information Disclosure Statement. Though that patent application does not specifically disclose or claim the high aspect ratio microcapsules of the present invention, its performance relative to the encapsulated versus non-encapsulated antimicrobial agents, is directly analogous to the instant claimed materials. The premise of the instant application is that the selection of the high aspect ratio microcapsules will provide added benefits over the lower aspect ratio microcapsules, such added benefit allowing for the use of even lower loadings of the microcapsules for the same degree of efficacy and/or longer longevity of antimicrobial activity due to the larger reservoir and the greater likelihood/probability of contact of the particle with the surface of the polymer substrate or coating into which it is incorporated owing to the high aspect ratio.

The comparative data set forth in the above-mentioned International Patent Publication clearly supports and demonstrates the unexpected and markedly increased performance of the antimicrobial agent when incorporated into a coating or polymer composition in a hydrophilic polymer encapsulated form. Furthermore, as recognized by those skilled in the art and as discussed in the background section of the instant specification, the hydrophilic coatings of Trogolo et. al. are limited in their utility, due to the very nature of hydrophilic polymers, and are not without a number of shortcomings. Typical hydrophilic coatings are soft and of low wear resistance; hence these coatings are inappropriate for applications which require a hard surface and/or good wear resistance. Similarly, hydrophilic coatings would be inappropriate for use on most articles that are subject to high moisture environments or a constant or intermittent flow of water as these coatings would quickly become depleted of their antimicrobial agent: the exception, of course, would be where the coated articles intended to have a short life such as a catheter.

By virtue of the invention claimed by the instant application, a means has now been found for taking advantage of the good aspects of hydrophilic materials when used in conjunction with antimicrobial agents, especially transportability of the antimicrobial active in the polymer matrix, without taking along the adverse aspects of the same, i.e., poor or limited utility and/or physical properties. Since the level of incorporation of the antimicrobial microcapsules in the matrix polymer is low, there is little, if any, impact on the performance or physical properties of the matrix polymers. Thus, one is able to prepare highly efficacious antimicrobial compositions using essentially whatever polymer matrix is needed for the given end-use application.

Furthermore, in addition to enhancing the release of the antimicrobial active from the non-hydrophilic matrix, the microparticles also serve as large reservoirs of the antimicrobial agent since multiple particles of the antimicrobial agent are dispersed in each high aspect ratio microparticle of the present invention. As set forth in the specification, when the inventive particles of the present invention are dispersed in a non-hydrophilic polymer matrix or coating, so long as a portion of the particle is very close to, touches or protrudes from the surface thereof, all of the antimicrobial agent in that particle is available to provide antimicrobial protection. By virtue of the microparticles having a larger size than the nonencapsulated antimicrobial agents and containing a plurality of particles of the antimicrobial agent itself, there is a greater likelihood that the microparticles of the present invention, having a large reservoir of the antimicrobial agent, will touch the surface, thus, enabling one to use less antimicrobial agent in a given amount of polymer for the same or better efficacy. This means significantly reduced costs, an issue of particular concern with the costly ion-exchange type antimicrobial agents.

In view of the foregoing, it is clear that Trogolo et. al. is not relevant or pertinent, from a patentability standpoint, to the subject matter of the present invention. Even if Trogolo et. al. is found pertinent; it is clear that Trogolo et. al. do not teach, suggest or motivate one with regard to, or in any way make obvious, the preparation of microparticles of the size and dimensions claimed or their utility as additives for polymer coatings and compositions, and particularly not the unexpected and markedly improved performance of the same. In any event, any presumption of obviousness has been fully rebutted. Consequently, the rejection based on Trogolo et. al. should be withdrawn and the application passed on to early and favorable consideration.

Claim Rejections – Section 103: Trogolo et. al. in view of Michal et. al.

Claims 1-22, 33-34 and 45 stand rejected under 35 USC §103(a) as being unpatentable over Trogolo et. al. (US 6,436,422) further in view of Michal et. al. (US 6,287,285). Trogolo et. al. is cited for the reasons set forth above. It is noted that Trogolo et. al. do not disclose the use of a dopant, particularly a sodium nitrate dopant. Michal et. al. is cited as showing the use of nitric-oxide donors, including sodium nitrate, as vasodilators in association with the use and implantation of medical devices. It is asserted that both Trogolo et. al. and Michal et. al. teach medical devices with a hydrophilic coating. The Patent Office thereby concludes that it would be obvious to have modified the composition of Trogolo et. al with a dopant, such as sodium nitrate, for the purpose of relaxing smooth muscle tissue as asserted by Michal et. al. The alleged expected result being a microcapsule comprising a hydrophilic polymer, an antimicrobial agent and a dopant.

Applicants respectfully traverse the rejection and request reconsideration. As noted above, Trogolo et. al. have nothing to do with the preparation of micro-sized, particulate, high aspect ratio microencapsulated antimicrobial agents, let alone to their use as additives for polymer coatings and compositions. Trogolo et. al. teach and claim coating compositions comprising a hydrophilic polymer and an antimicrobial agent for use in coating various substrates including, particularly, medical devices. Michal et. al. allegedly teach hydrophilic coatings containing therapeutic agents, especially nitric oxide donors such as sodium nitrate. The Patent Office then concludes that it would be obvious to combine the antimicrobial agent and the nitric oxide donor in a hydrophilic coating for the purpose of antimicrobial activity and the therapeutic activity of the nitric oxide donor. However, this premise, and the allegation of obviousness of the present invention in light thereof, fails and must be withdrawn.

First, as noted above, neither Trogolo et. al. nor Michal et. al. disclose, teach or suggest micro-sized particles, instead both teach liquid coatings. While Trogolo et. al. teach coatings comprising an antimicrobial hydrophilic polymer composition in a solvent, Michal et. al. teach coatings that are prepared in situ, by sequentially applying various layers or components of the coating materials to a substrate. Michal et. al. grafts or bonds its desired "active" through linking groups or a base layer previously applied to the substrate. The "active" may be a therapeutic agent, a diagnostic agent **or** a hydrophilic agent. (emphasis added) Nowhere does

Michal et. al. teach, suggest or motivate one to prepare or use or even to try to make or use a coating having any combination of the aforementioned agents, and certainly not a hydrophilic coating having a nitric oxide donor. Throughout Michal et. al. reference to these agents is always in the alternative, one can make a hydrophilic coating or a diagnostic coating or a therapeutic coating, but never is there a hint of a hydrophilic therapeutic coating. Indeed, in speaking of its preferred embodiment Michal et. al. state, "[I]n the presently preferred embodiments, the device is a polymeric catheter... having a hydrophilic coating of the invention, or the device is a metal device such as a stent coated with a therapeutic or diagnostic coating of the invention." Furthermore, Michal et. al. makes clear that hydrophilicity is not critical, if even pertinent, to the use of therapeutic agents, such as the nitric oxide donors, for Michal et. al. teach that the therapeutic materials may themselves be hydrophobic (see Col. 4, lines 13-25). It is also to be noted that the reference to nitric oxide donors is but one of a myriad of different therapeutic agents mentioned. Thus, it is clear that even Michal et. al. regard therapeutic agent modified coatings and hydrophilic coatings as being distinct and unrelated.

Finally, even if one were to accept the premise of the Patent Office, that one could combine Trogolo et. al. with Michal et. al., it is not clear what would motivate one to select only those certain nitric oxide donors which would participate in the ion-exchange process out of the many nitric oxide donors mentioned and, more significantly, out of the hundreds of therapeutic agents mentioned. While the Patent Office suggests that one would get coatings having both antimicrobial and vasodilating effects, there is nothing to support such a conclusion. One of the key aspects of Michal et. al. is that the therapeutic agent is chemically bonded into the coating material in order to avoid its quick depletion when placed in an aqueous environment or in-vivo. Trogolo et. al. provide no such reactivity or integration: their dopants are blended in so as to ensure that the dopant is free to participate in the ion-exchange process. Also, since the nitric oxide donor would be consumed in Applicants' invention, it is not clear what effect this may have upon the therapeutic value or properties of the nitric oxide donor. Consequently, those skilled in the art would more likely have avoided the use of those nitric oxide donors capable of participating in the ion-exchange process for fear of losing or significantly compromising the therapeutic effect.

As previously noted, nothing in either reference, alone or together, makes in any way obvious or in any way suggests or infers or motivates one to the preparation of micro-sized particles comprising a hydrophilic polymer containing an antimicrobial agent in combination with a dopant. Similarly, nothing suggests or in any way would contemplate that such a combination would provide a synergistic property relative to the release of the antimicrobial agent and, hence, the antimicrobial efficacy of a hydrophilic coating incorporating both. Thus, it is clear that the rejection based on Trogolo et. al. in view of Michal et. al. is without merit and/or has been fully rebutted. Applicants respectfully request that the rejection be withdrawn and the application passed on to allowance.

Conclusion

In light of the foregoing amendments and discussion, particularly the further clarification to the instant claims, it is believe that the rejections under 35 USC 103(a) have been fully addressed and rebutted. Consequently, Applicants believe the claims, as now presented, are in proper form for allowance. Early and favorable reconsideration is respectfully requested.

Fees

Although Applicants have added 1 new independent and a total of 16 new claims, resulting in 3 independent and 39 total claims, no additional fees are due as Applicants had originally paid for 4 independent claims and 46 total claims upon filing this application.

Applicants believe all matters raised in the Office Action have been fully addressed. Should there be any questions, please contact the undersigned, Applicant's attorney.

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